What Options Do We Have for Induction Therapy for Crohn's Disease?

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Key Words

Crohn's disease · Induction · Remission

Abstract

The first goal of Crohn's disease treatment is to induce a response. The choice of induction therapy depends on a number of factors. First, disease severity will dictate the level of intensity of treatment. Moderate to severely active Crohn's disease needs to be treated more aggressively than mild disease. Second, it is important to consider the disease distribution, since some medications (e.g. 5-aminosalicylates, budesonide, antibiotics) are more effectively delivered to the small bowel or the colon. Third, prior medications need to be considered. A patient naïve to immunomodulators and anti-TNF agents will be managed very differently from a patient who has already failed two anti-TNF drugs. A fourth critical factor is considering the individual patient. The balance of benefits and risks will depend upon the patient's expected disease course, and how much risk they are at personally for serious adverse events related to treatment. In addition, patients' preferences for treatment need to be addressed since they will choose therapies differently based on their personal experience with symptoms, thresholds for risk taking, and fears about their disease and treatment. The basic armamentarium for induction therapy for Crohn's disease in-

cludes: 5-aminosalicylates, antibiotics, budesonide, systemic corticosteroids, thiopurines, methotrexate, and anti-TNF agents. These drugs can be used alone or combined in different treatment algorithms to optimize therapy. The art of treating the IBD patient is in understanding the options and being able to apply an individualized regimen based upon unique patient and disease factors.

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Introduction

The first goal of treatment for patients with Crohn's disease is to induce a treatment response. Although the long-term objectives are to control inflammation, prevent complications and improve the overall quality of life, the initial choice of therapy will set the stage for the plan for maintenance of remission. There are a number of treatments for Crohn's disease that are used as induction therapy. Some medications are less effective but have very few side effects such as 5-aminosalicylate drugs (5-ASAs), while others have a high rate of treatment success but with the tradeoff of a high rate of adverse events such as systemic corticosteroids. The initial choice of therapy depends upon the severity of disease and required rapidity of action. For example, a patient who feels well but has a

high disease burden may be able to wait the necessary three or four months for immunomodulators to take effect, whereas a patient who is significantly symptomatic needs an immediate acting and effective agent. The induction agent chosen by the provider should match the nature of the disease and also the preferences of the patient based upon their perceptions of the balance of benefits and risks.

Options for Induction Therapy

The basic armamentarium for induction therapy for Crohn's disease includes: 5-ASAs, antibiotics, budesonide, systemic corticosteroids, thiopurines, methotrexate, and anti-TNF agents. These drugs can be used alone or combined in different treatment algorithms to optimize therapy. The approach to induction therapy can be categorized into three main groups: (1) corticosteroid induction, (2) steroid-free 'bridge' induction therapy to immunomodulators, and (3) anti-TNF induction.

Corticosteroid Induction

Prednisone is highly effective for inducing remission in patients with Crohn's disease. In the National Cooperative Crohn's Disease Study (NCCDS), a large randomized controlled trial from the 1970s, at the end of 15 weeks 60% of patients were in remission when treated with prednisone as compared to 30% of those in the placebo group ($p < 0.001$) [1]. There is not much debate about the effectiveness of corticosteroids for improving symptoms, but once initiated, the long-term outcomes are disappointing. In a cohort of patients from Olmsted County (Minn., USA) although over 80% of patients had either a complete or partial response to corticosteroids at 30 days, at the end of one year, only 28% had a prolonged response, 32% were steroid dependent, and 38% required surgery [2]. Even if patients respond, adverse effects are common. Approximately 50% of patients receiving corticosteroids stop taking this medication due to some side effect. Common events that are typically quickly reversible upon cessation of therapy include acne, moon facies, easy bruising, and ankle edema. More serious long-term problems related to steroid use include osteoporosis, cataracts and diabetes [3, 4]. Furthermore, in a recent population based study including almost 6,000 patients from the United Kingdom, the highest risk of death were in those patients treated with corticosteroids (HR 2.48, 95% CI 1.85–3.31). Although 'bias by indication' might be in part responsible (e.g. sicker patients received corticosteroids), the hazard

ratio of those receiving thiopurines was 0.83, and although not statistically significant to be protective it strengthens the argument of a detrimental effect of corticosteroids.

Prednisone-Free 'Bridge' Induction to Immunomodulators

Patients with Crohn's disease who have more than mildly active disease typically will receive immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) to maintain remission. Since there is a delay of onset of the effectiveness of these medications of approximately 2–4 months, some treatment is required to help induce remission while awaiting their effects. Although corticosteroids can be used to bridge this gap, as noted above, if possible, it is optimal to avoid systemic corticosteroid exposure.

Sulfasalazine was also studied in the NCCDS and compared to placebo for effectiveness in inducing remission [1]. At a dose of 1 g/15 kg, at week fifteen 43% of patients receiving sulfasalazine were in remission compared to 30% of those in the placebo group ($p = 0.08$). Although this just missed statistical significance, the authors noted that for the subgroup of patients with colonic disease, sulfasalazine appeared to be particularly effective. The other 5-ASA derivatives may not be as effective in Crohn's disease. Although one study showed mesalamine capsules (Pentasa) were effective for the treatment of active Crohn's disease [5], when this was combined with two other studies as part of a meta-analysis, the overall response was far from overwhelming [6]. At 16 weeks, although the mean reduction of the Crohn's Disease Activity Index (CDAI) was 63 points in the treatment group, the placebo group dropped 45 points. The comparison between groups was statistically significant ($p = 0.04$), but the difference of 18 CDAI points is considered not clinically important, and therefore has led to the abandonment of mesalamine for the treatment of Crohn's disease by many experts.

Budesonide is a corticosteroid with minimal absorption and therefore minimal systemic exposure. Based on its pH sensitive coating, this medication is delivered primarily to the ileum and right colon. With a side effect profile that is better than systemically absorbed corticosteroids, this is an appealing drug for the induction of remission of Crohn's disease. In a randomized controlled trial using budesonide at a daily dose of either 3, 9 or 15 mg, all compared to placebo, the 9 mg dose was superior at weeks 2 and 8 [7]. The rate of remission at two weeks was 33% in the budesonide group (compared to

11% for placebo) and 51% at week 8 (compared to 21% for placebo, $p < 0.001$). A study published in the same issue of the *New England Journal of Medicine* in 1994 compared budesonide to prednisolone for the induction of remission of Crohn's disease [3]. There was a small absolute difference in the remission rate between these two drugs at 10 weeks (53% budesonide group, 66% prednisolone group), but this was not statistically significant ($p = 0.12$). However, there was a significant difference in the frequency of side effects favoring budesonide ($p = 0.003$), suggesting that budesonide is nearly as effective as prednisolone but better tolerated.

Antibiotics have been studied for the treatment of Crohn's disease for years, but there is still uncertainty about their effectiveness. Sutherland et al. published a randomized controlled trial comparing metronidazole to placebo in patients with active Crohn's disease [8]. There was no difference in remission rates between the two groups, but there was a significant difference for improvement in the CDAI ($p = 0.001$). In a subgroup analysis of the data, it appears that this difference comes predominantly from the patients with colonic involvement, as there was not a difference seen in those with isolated small bowel disease. More recently rifaximin, a non-absorbable antibiotic, was evaluated in patients with active Crohn's disease [9]. At week 12 more patients in the rifaximin group responded to treatment. Although this did not reach statistical significance, the subgroup of patients with an elevated C-reactive protein who received rifaximin 800 mg twice daily did have significantly higher rates of remission and response as compared to placebo ($p < 0.05$).

In an effort to optimize the use of budesonide and antibiotics, Steinhart et al. evaluated the efficacy of budesonide on its own as compared to budesonide in combination with antibiotics (ciprofloxacin and metronidazole) [10]. There was no difference in remission rates at week 8 between the two groups. In a sub-group analysis of patients with colonic disease, although still not statistically significant ($p = 0.10$), there was a fairly large absolute difference in remission rates (53% with budesonide and antibiotics, 25% with budesonide alone). The small sample size of this sub-group limits the clear interpretation of these results, but intuitively the addition of antibiotics to budesonide in patients with Crohn's disease involving the ileum and colon may add some incremental benefit. Overall, there is no clear benefit of antibiotics for the treatment of Crohn's disease; however, there likely are subgroups of patients who will respond to these medications.

Anti-TNF Induction

Anti-TNF therapy offers a rapid onset of efficacy, which makes this class of medication an appealing induction agent while also allowing for the avoidance of corticosteroids. In the large registration trials for adalimumab, certolizumab pegol, and infliximab, the rate of responding to an induction regimen within the first few weeks of therapy is approximately equivalent across agents at about 60% [11–13]. Although not quite as high as the response rate of corticosteroids, these agents typically are well tolerated and are more effective than other treatments for inducing response or remission in patients with Crohn's disease. With that said, 40% of patients do not respond, which leaves a significant amount of room for improvement.

There have been a few strategies sought to improve the response rate of anti-TNF agents. First, the use of infliximab has been studied in a 'top-down' approach, by giving infliximab in combination with azathioprine to patients naïve to these medications and before using corticosteroids [14]. This top-down strategy yielded a 65% remission rate at week 14 compared to 30% in the standard 'step-up' approach of waiting to administer anti-TNF agents until patients have failed steroid withdrawal and immunomodulators. The SONIC trial further explored the question of the early use of anti-TNF medications and additionally studied the benefit of the combination of anti-TNF and immunomodulator therapy versus anti-TNF monotherapy [15]. Although the primary endpoint of the trial regarded maintenance of remission at week 26, even by 10 weeks there started to be a separation of the groups, with combination therapy showing superiority. One other important study approached this same question from a slightly different angle. The COMMIT study compared anti-TNF monotherapy to anti-TNF therapy combined with methotrexate [16]. All of these patients were also given prednisone for the induction period. Therefore, we see the results of 'triple-drug therapy' with an anti-TNF, immunomodulator and corticosteroids used concomitantly. In COMMIT, we see the highest rates of remission in any randomized controlled trial for Crohn's disease, with nearly 80% of patients in steroid-free clinical remission at week 14. From these series of studies, we learn that anti-TNF therapy is very effective for the induction of a treatment response and remission, and that adding an immunomodulator, and possibly prednisone, further enhances the rates of success.

Table 1. Options for Crohn's disease induction therapy

Mild endoscopic disease	Moderate-severe endoscopic disease
<i>Minimal symptoms</i> Budesonide for ileal disease and/or antibiotics for colonic disease or sulfasalazine for colonic disease	<i>Minimal symptoms ('rapid step-up')</i> IM at diagnosis and budesonide for ileal disease and/or antibiotics for colonic disease
<i>Moderate to significant symptoms</i> Systemic corticosteroids	<i>Moderate to significant symptoms</i> Systemic corticosteroids plus IM or Anti-TNF +/- IM or Anti-TNF + IM + corticosteroids
IM = Immunomodulator.	

Conclusions

There are a number of agents that can be used with success to induce a treatment response and remission for patients with active Crohn's disease. As reviewed above, some agents have more supportive data than others, and some are clearly more effective with or without the risk of added adverse events. The decision to use a particular agent or agents is based upon the individual patient. Clear algorithms that apply to all patients are difficult to produce based upon the numerous combinations of patient and disease variables. A recent RAND expert panel made recommendations on the use of anti-TNF agents with or without immunomodulators for the treatment of active Crohn's disease. To capture the different types of patients we treat in clinical practice, the panel developed 134 different patient scenarios [17]. Therefore, in addition to having to know the available induction treatment options, individualize choices have to be made based on the severity of their disease and current symptoms (table 1). Patients with mildly active endoscopic disease who are only minimally symptomatic have time to try medications that are safe which may or may not be effective. Patients with mild endoscopic disease but who are more bothered by symptoms can be treated with systemic corticosteroids with a high likelihood of treatment success. Patients with moderate to severely active endoscopic disease who are minimally symptomatic also have time to try induction therapy without the use of systemic corticosteroids or anti-TNF agents while awaiting the effects of immunomodulators. However, they should have a 'rapid step-up' approach, with a swift move to systemic corticosteroids or an anti-TNF agent if they are not quickly obtaining remission and mucosal healing. Patients with moderate to severely active endoscopic disease who are

more symptomatic should be treated with either anti-TNF monotherapy, combination therapy with an anti-TNF agent and an immunomodulator, or 'triple-drug' therapy adding systemic corticosteroids. These choices should be made together with patients, weighing the benefits against the risks, so that a shared decision can be made to best treat the individual patient.

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Dr. Siegel has served as a consultant and developed and delivered CME material for Abbott Labs, Elan Pharmaceuticals, and UCB. He has also served on the advisory board for P&G/Warner Chilcott.

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